Advances in Research

University of Michigan Kellogg Eye Center

From the Director

Dear Friends,

This issue of *Advances* appears just as we are finalizing design plans for the expansion of the Kellogg Eye Center. The new space will enable our research program to grow significantly, providing flexibility as we respond to emerging priorities.

We will gain 16,000 net square feet of laboratory space, nearly doubling what we have in the current building. With open laboratory design and many gathering areas, the new space will foster collaboration, collegial interaction, and a sense of community.

With flexible space, we can more easily bring in new resources for special projects and build the multidisciplinary teams that help accelerate the pace of research.

At the recent opening of the University's spectacular Biomedical Sciences Research Building, Nobel laureate and keynote speaker Thomas R. Cech, Ph.D., observed that research space should encourage what physicists refer to as "productive collision." Dr. Cech believes that something remarkable occurs when great scientific minds make contact with one another.

We expect our new research center to provide the perfect setting for productive collision, and much more.

Paul R. Lichter, M.D.
Director, University of Michigan
W.K. Kellogg Eye Center

University of Michigan
Kellogg Eye Center

photo by Peter Smith

photo by Lin Goings

Radha Ayyagari, Ph.D., and John Heckenlively, M.D., are developing new tests for inherited eye disease.

Genetic testing
helps physicians zero in on eye disease

Rapid genetic testing for eye disease is becoming a reality, thanks to a technology developed at the U-M Kellogg Eye Center. Scientists have created a first-of-its-kind test on a micro-chip array that will help physicians hone their diagnoses for patients with the blinding disease known as retinitis pigmentosa (RP). The screening technique has proven to be reliable and cost-effective.

In the September issue of *Investigative Ophthalmology & Visual Science,* Kellogg scientist Radha Ayyagari, Ph.D., reports on the arRP-I sequencing array, the first technology to screen simultaneously for mutations in multiple genes on a single platform.

This is a novel tool for scientists and physicians alike, says Dr. Ayyagari. "For diseases that are associated with multiple genes, like RP, we now have a new and faster method for identifying the underlying genetic basis. This can also be used to analyze complex patterns of inheritance and help us understand how causative genes might interact with each other."

Retinitis pigmentosa is a group of diseases, affecting 1 in 3500 individuals, in which retinal degeneration begins at a young age and leads to blindness or severe vision loss. Among the outward signs and symptoms are loss of peripheral vision, night blindness, and an abnormal electroretinogram, a test that measures the electrical activity and function of the retina. A patient with the autosomal recessive form of the disease (arRP) has inherited one mutated gene from each parent, neither of whom is affected by RP.

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Cutting through the data to cure eye disease

The Kellogg Eye Center continues to break new ground in vision genetics. But like others in this field, our scientists find themselves immersed in a sea of data that multiplies with each new discovery. More and more time is spent searching through data to find the nugget that is relevant to the research.

Kellogg has launched a new program, the Statistical Genetics Initiative, to tame the data overload and accelerate vision research. Thanks to a generous grant from the Edward T. and Ellen K. Dryer Foundation, the Eye Center is now recruiting a biostatistician who will help analyze data generated by faculty in the Department's 16 research laboratories. The new faculty member will hold a joint appointment in the School of Public Health.

A program that speeds the research process is good for the patient, says Paul R. Lichter, M.D., Chair of the Department. "Scientists must analyze seemingly endless combinations of genetic mutations before they can identify a disease-causing gene," he says. "If we can streamline that process, we'll know much sooner which genes put our patients at risk for diseases like macular degeneration, glaucoma, and diabetic retinopathy."

Key members of the initiative are **Kari Branham, M.S.**, genetic counselor, **Julia E. Richards, Ph.D.**, Associate Professor of Ophthalmology and Visual Sciences and Associate Professor of Epidemiology, and **Anand Swaroop, Ph.D.**, Harold F. Falls Collegiate Professor of Ophthalmology and Visual Sciences and Professor of Human Genetics.

photo by Robert Prusak

Philip J. Gage, Ph.D., is investigating a gene that regulates the development of the eye.

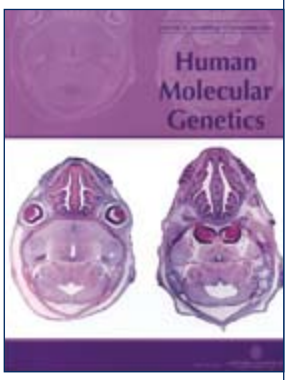
Gene may increase risk for early glaucoma

A gene that is pivotal to development of the eye may also lead to glaucoma in infants and young people. As scientist Philip J. Gage, Ph.D., learns more about the role of the gene, he believes that "developmental" or early-occurring glaucoma will yield clues to mechanisms at work in more common and widespread forms of the disease.

Glaucoma affects about 3 million people in the U.S., generally those over 40 years of age. If left untreated, the disease can cause permanent vision loss. There are many forms of glaucoma, but all involve damage to the optic nerve, the conduit that carries signals to the brain.

Dr. Gage explains that the gene *Pitx2* regulates eye development, instructing embryonic cells to begin forming fundamental structures of the eye. In the November 15 issue of *Human Molecular Genetics,* he reports that the gene must be present for the proper formation of several structures, including the optic nerve and ocular blood vessels. Using mouse models, he demonstrates how gene mutations could trigger disease.

The study is significant, explains Dr. Gage, because it proposes new mechanisms by which early-onset glaucoma can occur. "Patients with mutations in *Pitx2* may have other developmental eye defects that put them at a high risk for glaucoma," he says. "For example, they could have subtle defects that render the optic nerve susceptible to damage."



Because there are many forms of glaucoma, it is difficult to point to a precise cause. "Elevated eye pressure occurs in many but not all forms of the disease," explains Dr. Gage. "At the molecular level, we are beginning to suspect that factors like elevated pressure may have an indirect effect, exerting some kind of force on 'weak links' in the eye, such as the defects we found in our study."

Dr. Gage and graduate student and coauthor Amanda L. Evans are beginning the next phase of research: exploring how *Pitx2* regulates other genes and their biochemical pathways. They will continue to search for the mechanistic similarities among types of glaucoma; and they hope, eventually, to identify genes that can be targeted for treatment.

Giving a boost
to clinical research

This spring, a young physician-scientist at Kellogg will receive an award named for an alumnus who has made substantial contributions to the field of ophthalmology. The first Anthony P. Adamis, M.D. Scholar will receive support for clinical research that shows promise for advancing the understanding, treatment, or prevention of eye diseases.

The fund was established by Roberta W. Siegel, a patient who recognized from her first clinic appointment with Dr. Adamis that he was an outstanding individual. Having supported his earlier research, Mrs. Siegel conferred with Dr. Adamis as to where she might create a fund to honor his achievements. He suggested the U-M Department of Ophthalmology and Visual Sciences, where he completed his residency in ophthalmology. The idea had special appeal: Mrs. Siegel is a graduate of the University of Michigan as are several members of her family.

A new research award will honor alumnus Anthony P. Adamis, M.D.

Mrs. Siegel is delighted to assist in providing support for a young physician-scientist at the outset of his or her career. "I know that it takes considerable resources to start a research program, and I am pleased to have the opportunity to give young scientists a boost when they especially need it." Her interest in clinical research stems from observing how Dr. Adamis integrates patient needs into his research program.

Following his residency at Michigan, Dr. Adamis completed a clinical fellowship at the Massachusetts Eye and Ear Infirmary (MEEI) in Boston and did laboratory research with Judah Folkman, M.D. Dr. Adamis became an associate professor of ophthalmology at Harvard Medical School and Residency Program Director at the MEEI. He and a colleague were among the first to understand the role of the protein VEGF in blood vessel growth and leakage, a discovery of great significance for patients suffering from macular degeneration and diabetic retinopathy. From these discoveries, he co-founded Eyetech Pharmaceuticals, Inc., to develop novel therapeutics to treat eye diseases.

Department Chair Paul R. Lichter, M.D., recalls that Dr. Adamis had a keen interest in research when he applied for residency. "Tony has made very significant contributions to the field of ocular vascular disease," says Dr. Lichter. "We recognized his achievements when we asked him to deliver the Department's very first Distinguished Alumnus lecture in 1996. We are gratified that Mrs. Siegel, through her generosity, has given us an opportunity to recognize Dr. Adamis once again by establishing this prestigious award in his name. He serves as a superb role model for those who have the ambition to pursue a career as a physician-scientist."

Looking Ahead

Dr. Ayyagari is part of a national collaborative program that will provide patients with wider access to diagnostic genetic testing for eye disease. The program has tapped major research centers, like the University of Michigan, with laboratories that meet federal certification requirements for genetic testing.

Testing is expected to be available for retinal degenerations and forms of glaucoma and corneal dystrophies. The program will also provide data for scientists who are investigating genetic risk factors and gene-based therapies.

Watch the Kellogg website for news of this exciting program.

RP testing

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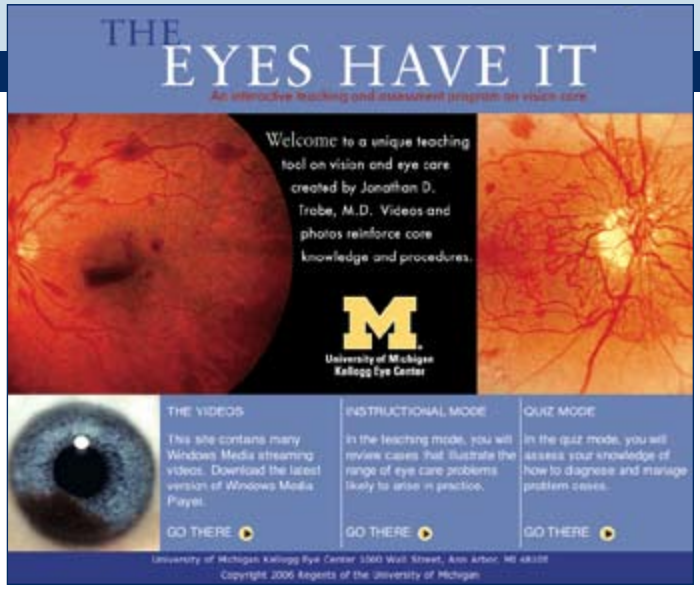
It is nearly impossible to identify which form of the disease a patient has through a clinical examination alone, notes John R. Heckenlively, M.D., a specialist in inherited eye disease who also participated in the study. "Identifying the precise genetic mutation responsible for an individual's disease will allow us to provide a precise diagnosis, and this knowledge will also allow us to apply genetic therapies as they are developed."

The arRP-I chip contains sequences, or genetic codes, of 11 genes that carry approximately 180 mutations associated with early-onset retinal degenerations. To date, more than 30 genes have been identified for various forms of RP. Dr. Ayyagari notes that while the size of the chip currently limits the ability to array all known RP genes, larger platforms are likely to be available soon. Additional testing is needed before the chip can be used for widespread testing.

Advances in Research

To learn more about the Kellogg Eye Center or if you wish to be added to our mailing list, contact the marketing staff at: aboutkellogg@umich.edu or 734.647.5586

THE EYES HAVE IT



A new interactive program serves as a short course in ophthalmology.

Medical students, unless they plan to become ophthalmologists, rarely spend enough time in eye care clinics. Yet many will specialize in pediatrics, family practice, and other specialties where they are sure to encounter patients with complicated eye disorders.

For these physicians and many other medical professionals, Jonathan D. Trobe, M.D., Professor of Ophthalmology and Visual Sciences, Professor of Neurology, and a well-known neuro-ophthalmologist and educator, has created a unique interactive teaching tool.

The Eyes Have It, now available at the Kellogg Eye Center web site, presents a wide range of typical and not so typical cases involving eye disease and trauma. Detailed photos illustrate the problem, and videos demonstrate how to perform basic procedures such as testing for near vision and eye alignment that will help define the problem and make a proper diagnosis.

A quiz for each section allows users to test their ability to diagnose and manage difficult cases. If users are unable to solve cases, they can call up the related teaching section for review, and then return to the quiz.

The interactive format and extensive use of videos make this a flexible and highly useable tool, says Dr. Trobe, author of the American Academy of Ophthalmology's popular textbook, *The Physician's Guide to Eye Care.*

The early reviews of the program are enthusiastic. Justin L. Gottlieb, M.D., ophthalmologist at the University of Wisconsin and an alumnus of ours, comments, "This is a very impressive teaching module which is right on target for the 'target' audience. It will be a terrific teaching aid for med students and others."

To review the site, please go to www.kellogg.umich.edu/theeyeshaveit

In this issue, read about genetic testing, a biostatistics initiative, glaucoma research, and new funding for clinical research

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